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Anxiolytic properties of *Melissa officinalis* and associated mechanisms of action: A review of the literature

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The anxiety disorders prevalence has significantly increased in society. These disorders can be treated with anxiolytics which, despite great efficacy, may result in several adverse side effects. Several studies have reported that anxiolytic effects result from the indirect action on the GABAergic system and mechanisms related to the cholinergic system. *Melissa officinalis* has been widely utilized for its sedative action and its ability to reduce agitation. Several studies using this plant in different experimental models have demonstrated its low toxicity and lack of side effects. Therefore, this study presents a literature review of the active principles responsible for the anxiolytic effect of *M. officinalis* and the mechanisms involved in this effect.

Key words: *Melissa officinalis*, lemon balm, anxiolytic action.

INTRODUCTION

According to the World Health Organization (WHO), approximately 80% of the world population uses traditional medicine based on empirical knowledge for primary health care (Taiwo, 2007). The use of plants in traditional medicine in Brazil is popular because of the natural diversity observed in the country and low costs the deepening and expansion of studies on herbal medicines have contributed to advances in this usage (Carvalho, 2011) and discovery of new drugs. *Melissa officinalis* was first described by Carolus Linnaeus in 1753 and initially cited in the French Pharmacopeain. It belongs to the Lamiaceae family and is a perennial lemon-scented herb in the mint family native to the Mediterranean and Southern Europe popularly known as lemon balm (Guginski, 2007). It was introduced to North America and can be found currently in gardens and

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roadside fields (Awad et al., 2009). This plant has been widely used because of its several therapeutic actions such as antioxidant (Dastmalchi, 2008; Pereira, 2009; Ribeiro and Bernardo-gil, 2001; Kamdem et al., 2014), anti-inflammatory, hepatoprotective (Birdane, 2007; Bolkent et al., 2005; Encalada et al., 2011), antibacterial, antifungal, antiviral, cholesterol-lowering (Bolkent et al., 2005), antitumor (Saraydin et al., 2012), anti-spas and antidepressant (L´opez et al., 2009).

The plant's sedative properties (Cases, 2011), including a reduction of stress, agitation, and anxiety (Kennedy, 2006) have been widely explored. It is believed that these properties could be related to the citral, which is one of its most abundant secondary metabolites (Lorenzi and Matos, 2002). Thus, as *M. officinalis* becomes a promising alternative to the treatment of anxiety, the understanding of factors that alter the bio-synthesis of citral is critical for a safer use of this herbal medicine.

The prevalence of anxiety disorders has significantly increased in the current society, with 10 million people currently suffering with this pathology (WHO, 2002) in Brazil. Anxiety disorders are usually treated through the use of drugs known as benzodiazepines. Benzodiazepines and barbiturates are the most commonly used despite their significant drawbacks such as physical dependence, tolerance, depression, and interference with memory mechanisms (Taiwo, 2007). Therefore, the search for alternative therapies that are as effective as those in use but with reduced adverse effects is of utmost importance (Baldwin and Ajel, 2007; Kennedy and Scholey, 2004; Millan, 2003; Sinclair and Nutt, 2007; Taiwo, 2007).

Traditional medicines are important options to meet the growing needs of health care; however, there is little scientific evidence ensuring their effectiveness and safety. This study reviewed the information published in the literature about the properties of *M. officinalis,* with the main focus on its anxiolytic roles and the major mechanisms of action involved.

METHODOLOGY

This study conducted an integrative literature review using articles that addressed the effects related to the anxiolytic properties of *M. officinalis* between 1994 and 2014 and indexed in the Scopus, Pubmed, Medline, and SciELO databases and SienceDirect. Eight articles that were published in the last eighteen years and addressed the anxiolytic activity of the plant in experimental models and one in a clinical evaluation were compared in this study.

RESULT AND DISCUSSION

M. officinalis L., Lamiaceae, popularly known as melissa or lemon balm is a perennial herbaceous species originated in Asia, North Africa, and Southern Europe where it is produced in large scale (Gurčik et al., 2005; Sorensen, 2000). Melissa is reproduced through branch cuttings or imported seeds and plants (Wanderer, 2004). Melissa leaves have been used since ancient times because of its action on the digestive system, mainly due to its carminative and vermifuge properties in the stomach, and as a tonic, antiseptic, and anti-inflammatory (Bertolucci et al., 2008; Sorensen, 2000). Another important use of its leaves and branches is as a condiment (Bertolucci et al., 2008; Carvalho et al., 2005; Couto, 2006).

Citral, citronellal, and geraniol are the main medicinal and condiment constituents in *M. officinalis*. These constituents are found in the essential oil obtained mainly from leaves that can yield between 0.02 and 0.37% of the majority of metabolites (MoradkhanI et al., 2010); the leaves are also used in infusion to produce teas. Hydroxycinnamic acids such as rosmarinic acid, and polyphenols such as tannins and flavonoids, are other constituents of *M. officinalis* reported to play important pharmacological roles (MoradkhanI et al., 2010; Sorensen, 2000).

In vitro studies showed that the essential oil from ethanol extracts of *M. officinalis* leaves contain several metabolites: tannin and rosmarinic derivatives, caffeic acid, flavonoids, and triterpenoid acids. Lorenzi et al. (2002) reported the following compounds as the major components: citronellal (1), citral (2), followed by β-caryophyllene (3), germancrene- D (4), ocimene (5), and citronellol (6) (Lorenzi and Matos 2002) (Figure 1).

Conversely, Allahverdiyev et al. (2004) showed that the most prevalent compounds are β–Cubebene, β–Caryophyllene (the only common compound between the studies), Sesquiterpene alcohol (C15H26O), α -Cadinol, Geranial (citral a), and Neral (citral b) (Table 1).

The different results in these two previous studies could come from the use of different extraction and identification methods; Allahverdiyev et al. (2004) used mass spectrophotometry ensuring greater reliability on the results because of the high sensitivity of this method compared to those using older identification methods. However, compounds other than those cited in the present article, such as rosmarinic acid (Boyadzhiev and Dimitrova, 2007), have been found indicating that a wide range of compounds in this plant could hinder the identification of all compounds in its composition. This could be the limiting factor for pharmacological descriptions in other articles found in the literature.

According to Lorenzi and Matos (2002), the anxiolytic action of *M. officinalis* results from the interaction of limonene and citral with GABAA, one of the two ionic channels activated by the ligand responsible for the mediation of γ-aminobutyric acid (GABA), assuming a similar benzodiazepine activity in the plant through nicotinic and muscarinic receptors that are in direct

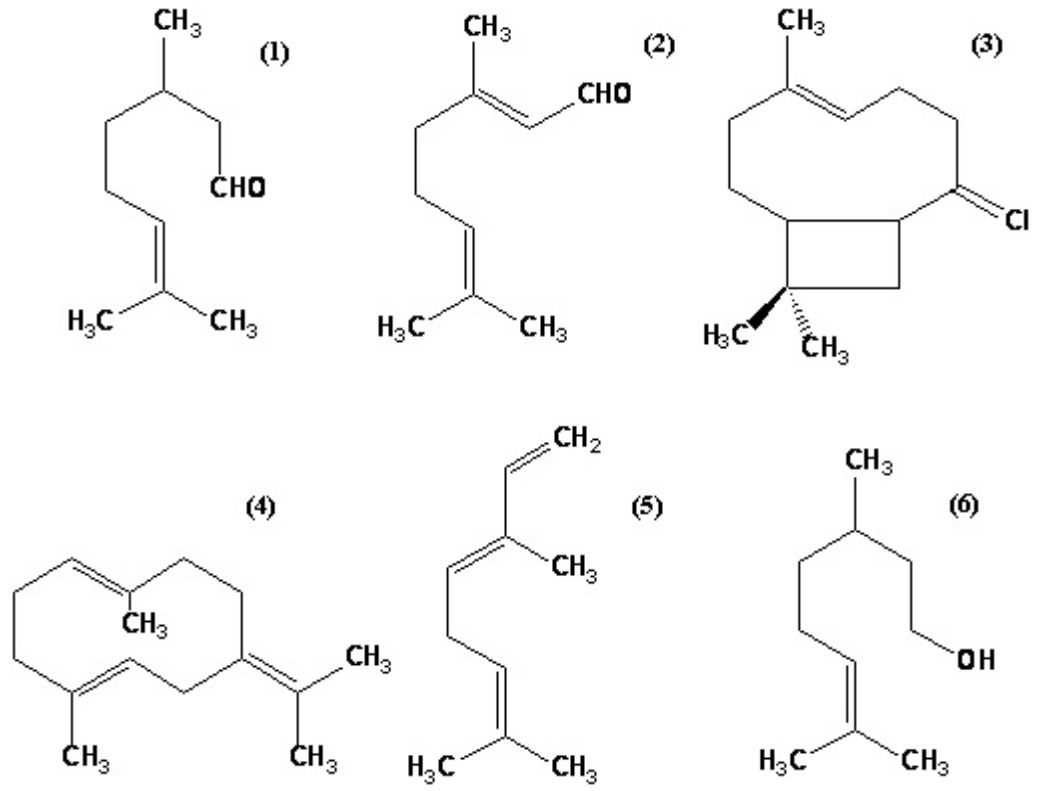

Figure 1. Chemical structure of the major components of *Melissa officinalis* leaves: citronellal (1), citral (2), β-caryophyllene (3), Germancreno-D (4), ocimene (5), and citronellol (6).

connection to the central nervous system (CNS). The study of Wake et al. (2000) working with *M. officinalis* and *Valeriana officinallis* to treat cholinergic receptors showed that the extract from the plant's leaves promoted connections at different levels in the two subtypes of these receptors; the level of connections was higher in the nicotinic subtype because the concentration of this receptor in the human occipital cortex is most expressive.

GABA is an inhibitory neurotransmitter of the central nervous system that reduces nerve impulse transmission between neurons through the hyperpolarization of postsynaptic membranes and the reduction of neuro-transmitter release into the synapse through presynaptic G-protein coupled receptor inhibition of voltage-gated Ca^{++} mechanisms (Weeks, 2009). The GABAergic system is well known as a modulator of cognitive function (Lewis et al., 2008; Menzies et al., 2007) and emotional behavior (Ibarra et al., 2010; Radley et al., 2009; Thoeringer et al., 2009). In this regard, Awad et al. (2009) have reported that rosmarinic acid in plants works by inhibiting the enzyme GABA transaminase (GABA-T), thereby increasing the levels of the neurotransmitter GABA and consequently, reducing anxiety. However, this would only be possible in a moderate stress state, because *M. officinalis* is not efficient when the stress level is severe (Ibarra et al., 2010). The GABAA receptors are ionic channels that mediate the effects of GABA, producing an inhibitory action through the opening of chloride channels preventing a neuronal action potential. This is seen as the mechanism of action of diazepam and is regarded as one of the possible mechanisms of action of *M. officinalis* (Abuhamdah et al., 2008; Akhondzadeh et al., 2003; Kennedy et al., 2002; Wecker and Catalano, 2006).

Wake et al. (2000) reported anxiolytic effects of *M. officinalis* on the CNS besides the proposed mechanism of specific metabolites connections in the herb, such as limonene and citral on the GABAA neurotransmitter. These effects occur through cholinergic receptors, where muscarinic receptors produce antagonistic effects especially on the M1 receptor. This receptor is located in the nerve ganglia and front-parietal cortex and acts by mediating excitatory postsynaptic potential due to stimulation of intracellular calcium entry (Gerber et al., 2001; López et al., 2009). Wake et al. (2000) analyzed Wistar rats in traditional behavioral models such as the Y-maze, social interaction test, forced swimming, and elevated cross maze and used tea from the leaves of *M. officinalis* as the testing sample. These authors demonstrated anxiolytic effects on the CNS through

Table 1. Percentage composition of identified compounds in *M. officinalis* total oil (Allahverdiyev et al. 2004).

Compound	%
β-Cubebene	15.41
β-Caryophyllene	14.24
Sesquiterpene alcohol ($C_{15}H_{26}O$)	7.39
α-Cadinol	7.18
Geranial (citral a)	6.62
Neral (citral b)	5.82
Cadinol isomer	3.96
trans-b-ocimene	3.96
β-Cadinene	3.62
Citronellal	2.92
β-Cedrene	2.53
α-Bisabolene	2.51
Nerolidol	2.36
Nonanal	2.34
α-Copaene	2.26
Calarene	2.12
γ-Elemene	1.7
Pinocamphone	1.34
Linalool	1.32
α-Cubebene	1.27
β-Elemene	0.89
1-Hepten-3-ol	0.5
6-Metyl- 5- heptene-2-one	0.42
Geraniol	0.38
cis-β-ocimene	0.37
Identified	93.43
Unidentified	6.57

the ingestion of high doses of plant extracts and teas, which did not induce respiratory depression or depressive attenuation at the level of the CNS frame. However, Coimbra (1994) pointed out that the treatment with *M. officinalis* essential oil in high doses can lead to mutagenic and neurotoxic effects.

Kennedy et al. (2002) used several concentrations of *Melissa's* essential oils (0.6, 1.2, and 1.8 g/kg/day) in humans to evaluate the anxiolytic action of *M. officinalis*, which occurs in the CNS by modulation of mood and cognitive processes. These authors reported that the most effective anxiolytic action was observed with the dose of 1.8 g/kg/day because it acted on the cholinergic system by decreasing stress and agitation in patients, thereby, confirming the proposed anxiolytic effect after ingestion of the plant's extract.

Wake et al. (2000) indicate that the main mechanism of action of *M. officinalis* extracts is based on its interaction with cholinergic receptors, the acetylcholine receptor (ACh). It is pointed out that *Melissa* will act displacing the molecule [3H] - (N)-nicotinic nicotinic, [3H] - (N)-escopolaminica, and muscarinic receptors by increasing ACh released after nerve stimulation in a mechanism that may be involved in improving cognitive function and reducing agitation. This hypothesis is not confirmed, and details of such a mechanism are still unknown.

Nevertheless, in contrast to Kennedy et al. (2002), Abascal and Yarnell (2004) reported in a randomized, double-blind trial control study using placebo with 20 healthy volunteers, that *M. officinalis* promoted an improvement in attention and stress reduction with a reduced dose (300 mg/kg/day) and decreased alertness and memory loss with an increased dose (900 mg/kg/day). However, the study failed to confirm significant cholinergic action.

Akhondzadeh et al. (2003) administered *M. officinalis* leaf extracts (600 mg/kg/day) to a group of Alzheimer's disease patients at mild to moderate stages of the disease. The study demonstrated that this treatment during 16 weeks resulted in a significant cognitive

improvement and reduction in the agitation experienced by some patients with this disease. This study demonstrates a possible effective treatment of Alzheimer's disease with *M. officinalis* resulting from modulatory actions on mood and cognitive performance, and on acetylcholine receptors in the CNS, following acute administration.

Nowadays, *M. officinalis* is not individually used as a pharmacological treatment for any disease. It is widely used in conjunction with another plant such as in Sonhare® whose pharmacogens from *Valeriana officinalis L*. and *M. officinalis L.* have therapeutic indications in relieving sleep difficulties, tension, restlessness, and irritability. The Sonhare® has a medication package and insert information sheet that do not inform which part of the plant is used or illustrate self-medication usage. Nevertheless, this is a controlled medication that is an excellent option in the prophilaxis of advanced stress (Moura, 2006).

There are few in-depth studies available reporting on the action in other systems on this subject because they failed to address pharmacological aspects. However, some can be cited such as the digestive system (Simmen et al., 2006; Schemann et al., 2006) in which the action can be linked to gastrointestinal motility reduction (Bolkent et al., 2005). Moreover, Sadraei et al. (2003) reported anti-spasmodic effects in the ileum due to one of its major components, indicating that *M. Officinalis* represents a good choice of herbal treatment for spastic episodes in the gastrointestinal system.

This plant can present a protective action in the hepatic system because of the presence of phenolic compounds (Simmen et al., 2006; Schemann et al., 2006). However, a study conducted by Müzell (2006) pointed that *M. officinalis* displayed hepatotoxic effects after toxicity was induced in mice by Acetaminophen, resulting in inhibition or modulation of the activity of cytochromes P450 conferred by flavonoids present in the plant, and enabling these to increase or reduce the concentrations of various therapeutic drugs in plasma (Hodek et al., 2002). In the same study, Müzell (2006) covered the renal system, seeking the possibility of its protection from the plant's activity; however, the results were unsatisfactory because the drug toxicity was intensified in this case.

Anti-inflammatory activity is also promoted by phenolic compounds present in the plant, such as flavonoids, that have the ability to inhibit the activity of monooxygenases, lipooxigenases, cyclooxygenases (Svobodová et al., 2003), oxidoredutases, and hydrolases such as the hyaluronate lyase that catalyzes the degradation of hyaluronic acid; inhibitions can be competitive in some cases or allosteric in others (Havsteen, 2002). The rosmarinic acid is among the variety of compounds cited or not by different authors, which has shown anti-inflammatory activity and inhibitory activity to 5-lipoxigense, 3R-hydroxysteroid dehydrogenase, and lipid peroxidation as reported by Nakazawa et al. (1998). This compound features astringent, antioxidant, and anti-inflammatory activity by inhibiting lipooxigenases and cyclooxygenases, antibacterial and antiviral activity, and antimutagenic effect (Pereira et al., 2005; Petersen and Simmonds, 2003).

In addition to the anti-inflammatory activity, the antiviral activity to *Herpex simplex* can be cited, which was reported for the first time by May and Willuhn (1978). In this context, Schnitzler et al. (2008) observed reduced viral replication activity when using *M. officinalis* oil *in vitro*.

Conclusion

The use of traditional medicine presents a significant risk to public health because of the lack of knowledge regarding drug interactions and possible toxic effects. Research studies assessing the clinical efficacy of plants are necessary. Based on this literature review, it was concluded that extracts of *M. officinalis* have effective anxiolytic activity in reducing stress and physiological disturbances due to its direct interaction with the CNS and the cholinergic and GABAergic systems. Its mechanism of action is still controversial. Some authors suggest it is active on the GABAergic system and others on the cholinergic system. Abascal and Yarnell (2004) report no significant action on the cholinergic system while Wake et al. (2000) indicate that the main mechanism of action of *M. officinalis* is based on its interaction with cholinergic receptors.

Conflict of interest

Authors declare that there are no conflicts of interest

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